

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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SUBJECT: 2006 Update: Post-Pediatric Exclusivity Postmarketing Adverse Event Review  
Drug: Atorvastatin (Lipitor®), NDA# 020702  
Pediatric Exclusivity Approval Date: February 22, 2002

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## 1. EXECUTIVE SUMMARY

This document updates a previous Office of Surveillance and Epidemiology consult from 2003 that assessed atorvastatin pediatric reports during the one-year post-pediatric exclusivity period (2/22/02-3/22/03).<sup>1</sup> During this period, the AERS database did not contain atorvastatin pediatric reports so the participants at the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee (held June 12, 2003) requested additional follow up.<sup>2</sup>

Atorvastatin was approved in December 1996, and granted pediatric exclusivity on February 22, 2002. In pediatric patients (boys and postmenarchal girls [10 to 17 years of age]) atorvastatin is indicated as adjunct to diet to manage heterozygous familial hypercholesterolemia. Atorvastatin is classified as Pregnancy Class X, and the recommended pediatric starting dose is 10 mg daily and a maximum daily dose of 20 mg.

A search of the AERS database since the last OSE consult (March 22, 2003 through August 22, 2006) identified 8,013 atorvastatin reports (crude counts), of which 12 (six from the United States) were reported in children less than 17 years of age. Fifty percent of the reports (n=6) indicated the child (median age: 15 years old; range: 4-16 years) was using atorvastatin for hypercholesterolemia or cardiovascular indication, while the remaining 6 reports were associated with in utero exposure (n=3) or accidental ingestion (n=3).

In those six children using atorvastatin for hypercholesterolemia or cardiovascular indication, there were two reports of (based on MedDRA System Organ Class) **Blood and Lymphatic Disorders** (one report of iron-deficiency anemia in a 16-year-old girl and one report of bone marrow suppression in a 14-year-old with unknown medical history), two reports of **Respiratory, Thoracic and Mediastinal Disorders** (one report of bronchospasm with positive rechallenge in a 4-year-old boy, and one report of hemoptysis due to pulmonary alveolar hemorrhage) that occurred in a 16-year-old boy with heart failure. There was one **Gastrointestinal Disorder** report (16-year-old girl with diabetes and high cholesterol who was taking an oral contraceptive and developed pancreatitis about two years after starting atorvastatin) and one **Musculoskeletal and Connective Tissue Disorder** report (14-year-old boy on simvastatin for two years who developed thigh stiffness and CK of 792 after his methylphenidate dose was increased. Simvastatin was discontinued and the symptoms resolved. The boy was then switched to atorvastatin, and ezetimibe added. About 9 months later, the boy complained of muscle symptoms and the CK was 24,265. Atorvastatin and ezetimibe were discontinued and a month later the CK was 218).

Three reports involved **in utero exposures**. The first involves a woman on atorvastatin for about a year, which was discontinued 8 weeks into her pregnancy. The woman reported her male infant was born blind. The second report involves a 34-year-old female with gestational diabetes mellitus who was taking atorvastatin (duration unknown) and hypoglycemics. The fetus developed a single functional kidney, congenital hepatomegaly and stillbirth. The third report involves a 32-year-old man who took atorvastatin 10 mg daily two to three months before conception, and reported his daughter was "born with myopathy." Statins, including atorvastatin, are contraindicated

during pregnancy (Pregnancy Category X) because of their ability to lower cholesterol and cholesterol byproducts necessary during fetal development.

Three reports involved **accidental ingestion** of atorvastatin. The first involved a 14-year-old boy who took some of his father's medications (including atorvastatin, gemfibrozil, metformin, verapamil, and oxycodone). The child was admitted to the hospital for one night; the glucose was 83 and treated with 10 percent dextrose. The second involved a 2-year-old girl who experienced two seizures following possible ingestion of rosiglitazone, bupropion, metformin and atorvastatin. No evidence of toxic exposure was identified by the physician. The third report involved a 10-year-old girl who mistakenly received a package of atorvastatin (instead of or in addition to phenytoin) and took one dose daily for three days. On the third day, the child experienced "syncope crisis" and was admitted to the hospital. The child continues on phenytoin.

There was one report of pediatric death (stillbirth, described above) associated with maternal atorvastatin use and gestational diabetes mellitus.

The review of the few atorvastatin pediatric reports in the AERS database did not identify adverse events unique to the pediatric population. However, the review was limited by the few number and incompleteness of reports. In all of the cases, the reported adverse event could possibly be attributable to other causes. For example, the iron deficiency anemia that developed in the 16-year-old girl taking atorvastatin could also possibly be due to increased iron demand due to rapid growth, decreased iron intake or absorption, or increased iron loss due to menses.

In adults, liver dysfunction and muscle-related events are known, labeled risks associated with all statins. The National Lipid Association Safety Assessment Task Force<sup>9</sup> recently concluded: 1) Dose-related, asymptomatic elevations in ALT or AST more than three times the upper limit of normal are seen with all statins. These elevations are typically transient and resolve spontaneously. 2) Liver dysfunction or liver failure associated with statin use cannot be ruled out. FDA has received reports of liver dysfunction and liver failure associated with statins. It is possible liver failure is an idiosyncratic reaction that occurs very rarely with statin therapy, but it is also argued that the rate of liver failure in those individuals taking statins is about the same as the population not taking statins. 3) The most prevalent and significant adverse events associated with statin therapy are related to muscle symptoms or signs. Myalgia is the most common muscle symptom, and more likely to occur at higher statin doses or other situations resulting in elevated blood statin levels. Serious muscle toxicity associated with statin therapy is rare. 4) For individuals requiring statin therapy, the benefit outweighs the risk.

The current labeling for atorvastatin outlines liver, muscle, and pregnancy risks, and provides recommendations for monitoring and managing these risks.

In conclusion, the benefit of statins in adults is well documented, and there is growing evidence that statins are efficacious and well tolerated in the pediatric population. However, liver and muscle adverse events remain important risks associated with statin therapy. In addition, it is likely that pediatric patients who require lipid-lowering drugs

may use these drugs for many years, and the long-term safety profile of statins (including use during the growth period) is unknown. There are too few reported adverse events in any one area to make a conclusion regarding safety signals unique to the pediatric population. The Division of Drug Risk Evaluation will continue to monitor.

## 2. INTRODUCTION

This document updates a previous (2003) Office of Surveillance and Epidemiology (OSE) consult regarding the one-year post-pediatric exclusivity adverse event review for atorvastatin.<sup>1</sup> During the one-year post-pediatric exclusivity period, the AERS database did not contain atorvastatin pediatric reports so the participants at the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee (held June 12, 2003) requested additional follow up.<sup>2</sup>

## 3. PRODUCTS, INDICATIONS, PEDIATRIC LABELING, AND PEDIATRIC FILING HISTORY

### 3.1. Atorvastatin Products Available in the United States (Table 1)<sup>3</sup>

<b>Table 1. Description of Atorvastatin Products Available in the United States.</b> Source: 8/7/2006 Approved Labeling			
<b>Product</b>	<b>NDA</b>	<b>US Approval Date</b>	<b>Tablet Strengths</b>
Atorvastatin (Lipitor®)	020702	12/17/1996	10, 20, 40, 80 mg
Amlodipine/Atorvastatin (Caduet®)	021540	1/30/2004	2.5/10, 2.5/20, 2.5/40; 5/10, 5/20, 5/40, 5/80; 10/10, 10/20, 10/40, 10 mg/80 mg

<sup>1</sup> Chang J. Avigan M. ODS Postmarketing safety review: one-year post pediatric exclusivity postmarketing adverse events review for atorvastatin (PID D030178). 2003 Jun 5:1-4

<sup>2</sup> FDA-CDER. Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee. Adverse event reports as per Section 17, BPCA. 2003 Jun 12. Available at: <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3965T2.htm>.

<sup>3</sup> FDA/CDER (Drugs@FDA). Atorvastatin (Lipitor and Caduet) Approved Labeling. Silver Spring (MD): Food and Drug Administration. c2006 – [cited 2006 Aug 23]. Available from: [www.accessdata.fda.gov/scripts/cder/drugsatfda](http://www.accessdata.fda.gov/scripts/cder/drugsatfda).

### 3.2 Atorvastatin Approved Indications (Table 2)<sup>3</sup>

Table 2 describes FDA-approved indications for atorvastatin (Lipitor).

<b>Table 2. Atorvastatin (Lipitor) Approved Indications.</b> Source: 8/7/2006 Approved Labeling.
Prevention of cardiovascular disease in adults without clinically evident coronary heart disease, but with multiple risk factors, to reduce risk of: <ul style="list-style-type: none"><li>▪ Myocardial infarction</li><li>▪ Stroke</li><li>▪ Revascularization procedures and angina</li></ul>
Hypercholesterolemia <ul style="list-style-type: none"><li>▪ As adjunct to diet to reduce total-C, LDL-C, apo B, and TG levels and increase HDL-C in patients with primary heterozygous familial and nonfamilial hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb)</li><li>▪ As adjunct to diet to reduce elevated serum TG levels (Fredrickson Type IV)</li><li>▪ Treatment of primary dysbetalipoproteinemia (Fredrickson Type III) in those not responding to diet</li><li>▪ Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as adjunct to other lipid-lowering therapies or if such treatments are unavailable</li><li>▪ Adjunct to diet to reduce total-C, LDL-C and apo B levels in <b>boys and postmenarchal girls (10 to 17 years of age) with heterozygous familial hypercholesterolemia</b> if after trial of diet therapy the following are present:<ul style="list-style-type: none"><li>a. LDL-C remains <math>\geq 190</math> mg/dL, or</li><li>b. LDL-C remains <math>\geq 160</math> mg/dL and there is a positive family history of premature cardiovascular disease OR two or more other CVD risk factors are present in the pediatric patient</li></ul></li></ul>

### 3.3 Pediatric Labeling

#### 3.3.1 Pediatric Mentions in Atorvastatin Labeling

Clinical Pharmacology, Special Populations, *Pediatric*:  
Pharmacokinetic data in the pediatric population are not available.

Clinical Pharmacology, Clinical Studies:  
**Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)**

LIPITOR is effective in a wide variety of patient populations with hypercholesterolemia, with and without hypertriglyceridemia, in men and women, and in the elderly. Experience in pediatric patients has been limited to patients with homozygous FH.

#### **Heterozygous Familial Hypercholesterolemia in Pediatric Patients**

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia were randomized to LIPITOR (n=140) or placebo (n=47) for 26 weeks and then all received LIPITOR for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level  $\geq 190$  mg/dL or 2) a

baseline LDL-C  $\geq$  160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5-385.0 mg/dL) in the LIPITOR group compared to 230.0 mg/dL (range: 160.0-324.5 mg/dL) in the placebo group. The dosage of LIPITOR (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was  $>$  130 mg/dL. The number of LIPITOR-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%). LIPITOR significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase.

**Lipid-altering Effects of LIPITOR in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia  
(Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)**

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
LIPITOR	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0-242.0 mg/dL) in the LIPITOR group compared to 228.5 mg/dL (range: 152.0-385.0 mg/dL) in the placebo group during the 26 week double-blind phase.

The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of LIPITOR therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

**Indications and Usage. *Hypercholesterolemia***

Lipitor is indicated:

4. as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
  - a. LDL-C remains  $\geq$  190 mg/dL or
  - b. LDL-C remains  $\geq$  160 mg/dL and:
    - there is a positive family history of premature cardiovascular disease or
    - two or more other CVD risk factors are present in the pediatric patient

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	$<$ 170	$<$ 110
Borderline	170-199	110-129
High	$\geq$ 200	$\geq$ 130

## Precautions, **Pregnancy Category X**

### Precautions, Pediatric Use

Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months duration in adolescent boys and postmenarchal girls. Patients treated with LIPITOR had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls (see CLINICAL PHARMACOLOGY, Clinical Studies section; ADVERSE REACTIONS, Pediatric Patients (ages 10-17 years); and DOSAGE AND ADMINISTRATION, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on LIPITOR therapy (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy). **LIPITOR has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients (see CLINICAL PHARMACOLOGY, Clinical Studies: Homozygous Familial Hypercholesterolemia).

### Adverse Reactions, Pediatric Patients (ages 10-17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of LIPITOR 10 to 20 mg daily was generally similar to that of placebo (see CLINICAL PHARMACOLOGY, Clinical Studies section and PRECAUTIONS, Pediatric Use).

### Dosage and Administration

#### **Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)**

The recommended starting dose of LIPITOR is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines<sup>1</sup>, CLINICAL PHARMACOLOGY, and INDICATIONS AND USAGE). Adjustments should be made at intervals of 4 weeks or more.

## **3.3.2 Safety-Related Updates to Product Labeling Since March 22, 2003 OSE Consult**

### Patient Package Insert (PPI)

FDA approved a Patient Package Insert for Lipitor in May 2004, which was updated in June 2006 (available at: <http://www.fda.gov/cder/foi/label/2006/020702s046Pi.pdf>). Below are three sections from the PPI that contain mention of children.

#### **What is LIPITOR?**

LIPITOR is a prescription medicine that lowers cholesterol in your blood. It lowers the "bad" cholesterol and triglycerides in your blood. It can raise

your "good" cholesterol as well. LIPITOR is for adults and **children** over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone. LIPITOR starts to work in about 2 weeks.

#### **Who Should Not Take LIPITOR?**

Lipitor has not been studied in **children** under 10 years of age.

#### **How do I store Lipitor?**

Keep LIPITOR and all medicines out of the reach of **children**. Be sure that if you throw medicine away, it is out of the reach of **children**.

### **3.4 Pediatric Filing History**

Table 3 below contains relevant regulatory activity for the pediatric use of atorvastatin.

<b>Table 3. Relevant Regulatory Activity for Pediatric Use of Atorvastatin</b>	
<b>Date</b>	<b>Regulatory Activity</b>
6/12/03	Pediatric Advisory Subcommittee meeting for atorvastatin and simvastatin <sup>2</sup>
2/22/02	Pediatric exclusivity granted
9/6/99	Written Request issued for sponsor to conduct a clinical study in pediatric boys and girls with heterozygous familial hypercholesterolemia to characterize the efficacy and safety of atorvastatin. <sup>4</sup>

## **4. AERS SEARCH RESULTS**

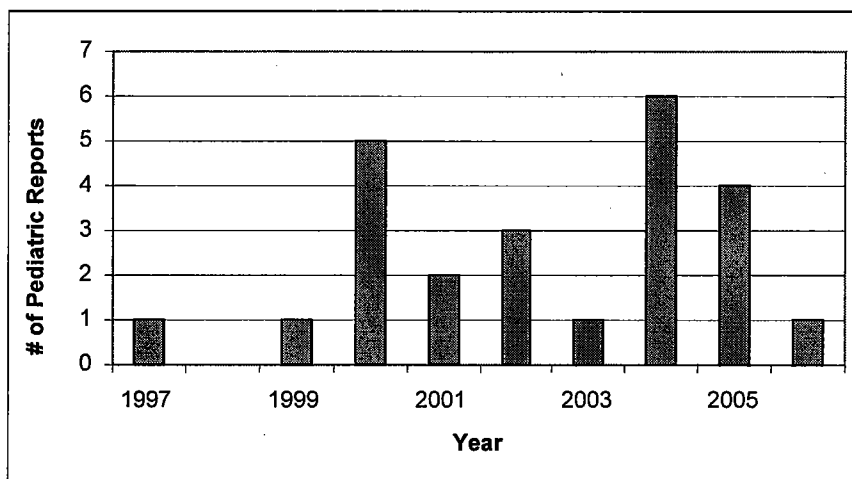
### **4.1 Count of Reports: AERS Search Including All Sources (U.S. & Foreign)**

<b>Table 4. Crude counts* of Atorvastatin Reports in the AERS Database for All Sources from March 22, 2003 (previous OSE consult) through August 22, 2006</b>			
<b>Age</b>	<b>All reports (US)</b>	<b>Serious† (US)</b>	<b>Death (US)</b>
Adults (≥ 17 yrs)	6,229 (3,312)	5,986 (3,090)	456 (131)
Peds (0-16 yrs)	12 (6)	12 (6)	1 (0)
Age Unknown (Null)	1,772 (1,357)	1,708 (1,296)	128 (75)
Total	8,013 (4,667)	7,706 (4,392)	585 (206)
*May include duplicates			
†Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.			

<sup>4</sup> Parks M, Orloff D. DMEP Medical Team Leader's memo on supplemental new drug application. 2002 Oct 1. Available at: <http://enterprisearch.fda.gov/index.htm>

<b>Table 5. Crude counts* of Atorvastatin Reports in the AERS Database for All Sources Since Approval (December 17, 1996) through August 22, 2006</b>			
<b>Age</b>	<b>All reports (US)</b>	<b>Serious† (US)</b>	<b>Death (US)</b>
Adults (≥ 17 yrs)	15,594 (8,874)	13,204 (6,775)	1,072 (271)
Peds (0-16 yrs)	24 (15)	23 (14)	1 (0)
Age Unknown (Null)	5,824 (4,570)	4,248 (3,213)	287 (170)
Total	21,442 (13,456)	17,475 (10,002)	1,360 (441)
*May include duplicates			
†Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.			

**Figure 1: Reporting Trend For Atorvastatin Pediatric Reports (approval date through 8/22/2006)**



## 5. POSTMARKETING REVIEW OF PEDIATRIC ADVERSE EVENT REPORTS

### 5.1 Case Characteristics:

<b>Table 6. Characteristics of Pediatric Atorvastatin Reports in the AERS Database (marketing approval through 8/22/06)</b>			
<b>Characteristic</b>	<b>Marketing To Previous OSE Consult (12/17/96-03/22/03)</b>	<b>Previous OSE Consult to AERS Cutoff Date (03/22/03-08/22/06)</b>	<b>Total Reports (12/17/96-08/22/06)</b>
<b>Number of Unique Reports</b>	<b>12</b>	<b>12</b>	<b>24</b>
<b>Origin of Reports</b>			
United States	9	6	15
Foreign	3	6	9
<b>Year (FDA Receive Date)</b>			
1997	1	-	1
1998	0	-	0
1999	1	-	1
2000	5	-	5
2001	2	-	2
2002	3	-	3
2003	-	1	1
2004	-	6	6
2005	-	4	4
2006	-	1	1
<b>Gender</b>			
Male	5	5	10
Female	3	6	9
Unknown	4	1	5
<b>Age At Time of Event</b>			
0 - <1 month	8	3	11
1 month - 2 years	0	1	1
3 - 5 years	0	1	1
6 - 11 years	1	1	2
12 - 16 years	3	6	9
Unknown	0	0	0
<b>Indication For Use</b>			
Accidental Ingestion	1	3	4
Hypercholesterolemia	3	5	8
In Utero Exposure	8	3	11
Myocardial ischemia	0	1	1
Unknown Indication	0	0	0
<b>Dose (Those Using For Dyslipidemia or Cardiovascular Indication)</b>			
10 to 20 mg	2	5	7
30 mg	0	1	1
Unknown	1	0	1
<b>Dose (Accidental Ingestions)</b>			
10 to 20 mg	0	1	1
40 mg	1	0	1
Unknown	0	2	2
<b>Dose (In Utero Exposures)</b>			
10-20 mg	2	1	3
40 mg	1	1	2
Unknown	5	1	6

**Table 6. Characteristics of Pediatric Atorvastatin Reports in the AERS Database (marketing approval through 8/22/06)**

Characteristic	Marketing To Previous OSE Consult (12/17/96-03/22/03)	Previous OSE Consult to AERS Cutoff Date (03/22/03-08/22/06)	Total Reports (12/17/96-08/22/06)
<b>Duration (Those Using For Dyslipidemia or Cardiovascular Indication)</b>			
< 6 months	1	0	1
6 – 12 months	0	3	3
>12 months	1	1	2
Unknown	1	2	3
<b>Duration (Accidental Ingestions)</b>			
≤ one dose	1	1	2
3 doses	0	1	1
Unknown	0	1	1
<b>Duration (In Utero Exposures)</b>			
At time of conception (paternal use)	1	1	1
First trimester	6	1	7
Unknown	1	1	2
<b>Primary Reported Adverse Event (by System Organ Class [SOC])</b>			
<i>Blood and Lymphatic Disorder</i>			
Bone Marrow Suppression	0	1	1
Fatigue/Iron Deficient Anemia	0	1	1
<i>Gastrointestinal Disorder</i>			
Gastrointestinal Upset (and dizziness)	1	0	1
Pancreatitis	0	1	1
<i>Hepatobiliary Disorder</i>			
Increased LFTs	1	0	1
<i>Musculoskeletal and Connective Tissue Disorder</i>			
Increased CK	0	1	1
<i>Nervous System Disorder</i>			
Depression, Exacerbated	1	0	1
<i>Respiratory, Thoracic and Mediastinal Disorder</i>			
Bronchospasm	0	1	1
Pulmonary Alveolar Hemorrhage	0	1	1
<i>Other</i>			
Accidental Ingestion	1	3	4
In Utero Exposures	8	3	11
Cleft Palate	(2)	-	2
Prematurity	(2)	-	2
Blindness	-	(1)	1
Choroid Plexus Cysts (normal infant)	(1)	-	1
Esophageal Atresia and Fistula	(1)	-	1
Left Arm Aplasia	(1)	-	1
Myopathy	-	(1)	1
Respiratory Distress	(1)	-	1
Stillbirth, Congenital	-	(1)	1
Hepatomegaly and Single Functional Kidney			

Continued on following page

<b>Table 6. Characteristics of Pediatric Atorvastatin Reports in the AERS Database (marketing approval through 8/22/06)</b>			
<b>Characteristic</b>	<b>Marketing To Previous OSE Consult (12/17/96-03/22/03)</b>	<b>Previous OSE Consult to AERS Cutoff Date (03/22/03-08/22/06)</b>	<b>Total Reports (12/17/96-08/22/06)</b>
<b>Reported Outcomes</b> (may not sum due to reporting of more than one outcome)			
Congenital Anomaly	5	2	7
Death	0	1	1
Disability	0	1	1
Hospitalization	2	4	6
Life-Threatening	0	0	0
Required Intervention	1	0	1
Other	4	8	12
Unknown/Not Reported	1	0	1

## 5.2 Summary of Cases Received

Since the previous OSE consult on March 22, 2003, FDA received 12 pediatric atorvastatin reports. Six of the 12 reports were from the United States and six were foreign reports.

Six reports involved adverse events in the following MedDRA System Organ Class (SOC) areas: Blood and Lymphatic Disorder (2), Respiratory, Thoracic and Mediastinal Disorder (2), Gastrointestinal Disorder (1), and Musculoskeletal and Connective Tissue Disorder (1). In these six reports, atorvastatin was prescribed for hypercholesterolemia (5) and myocardial ischemia (1). The remaining six reports involved in utero exposures (3) and accidental ingestion (3).

The first **Blood and Lymphatic Disorder** report (**CASE 5697315**) involves a 16-year-old girl with familial hypercholesterolemia (but no history of nutritional deficiencies) who experienced iron deficient anemia about a year after starting atorvastatin. The girl was treated with iron supplements and remains on atorvastatin. Other potential causes of the girl's iron-deficiency anemia include increased iron demand due to rapid growth during adolescence, decreased iron intake or absorption, or increased iron loss due to menses or blood loss. The second report (**CASE 4188752**) involves a 14-year-old patient (gender unknown) who was taking atorvastatin 20 mg (duration unknown) and experienced bone marrow suppression. This case was reported by a physician to a pharmaceutical sales representative, and lacked pertinent information (including medical history and concurrent medications) to assess causality. Thrombocytopenia and anemia (not specified as iron-deficiency anemia or bone marrow suppression) are in the atorvastatin labeling (occurring in less than 2 percent of patients [see ADVERSE REACTIONS]).

The first **Respiratory, Thoracic and Mediastinal Disorder** report (**CASE 5659245**) involves a 4-year-old boy with myocardial ischemia (on clopidogrel and aspirin) who was taking both atorvastatin (10 mg daily since Apr04) and simvastatin (20 mg daily since Mar04). The boy developed marked bronchospasm, which was reversible and "present 3

times on rechallenge.” The boy recovered from the bronchospasm in May04, but the outcome of simvastatin and atorvastatin use is unknown. It is possible the child experienced an allergic-type reaction, but the report lacked pertinent information (such as laboratory testing, exposure-time interval, or other medical history). The second (CASE 5720150) involves a 16-year-old boy with familial hypercholesterolemia who was hospitalized with hemoptysis after taking atorvastatin (dose increased from 10 mg to 20 mg) and nicotinic acid for about 6 months. On admission, the bronchoscopy showed diffuse pulmonary alveolar hemorrhage and the echocardiogram showed cardiomegaly with ejection fraction of 37 percent. Atorvastatin and nicotinic acid were discontinued. It is possible the hemoptysis developed secondary to the boy’s heart failure, but it may also be idiopathic or drug-induced. Bronchospasm and hemoptysis or pulmonary alveolar hemorrhage are not labeled events for atorvastatin. However, according to the labeling, sinusitis and pharyngitis were reported inconsistently in placebo-controlled studies; bronchitis and rhinitis occurred in  $\geq$  two percent of clinical trial patients; and pneumonia, dyspnea, asthma, and epistaxis occurred in less than two percent of clinical trial patients.

The **Gastrointestinal Disorder** report (CASE 5952060) involves a 16-year-old girl with diabetes and high cholesterol who experienced pancreatitis about two years after starting atorvastatin. The patient’s mother reported that “it seemed to go away,” but “came back” about two months later. The girl was also taking an oral contraceptive (unspecified), homeopathic detox and pain medications. Pancreatitis is in the atorvastatin labeling, occurring in less than 2 percent of patients [see ADVERSE REACTIONS]). It is not clear from the report if the 16-year-old girl developed acute or chronic pancreatitis (or if her diabetes was induced by chronic pancreatitis). Most acute pancreatitis is caused by biliary disease such as gallstones (30 to 60 percent of cases) or alcohol use (15 to 30 percent of cases), but about 2 to 5 percent of cases is induced by drugs such as estrogen-containing oral contraceptives.<sup>5</sup> The atorvastatin labeling indicates co-administration of atorvastatin and an oral contraceptive increases the area under the curve (AUC) for ethinyl estradiol (20 percent) and norethindrone (30 percent). Individuals with diabetes mellitus may develop hypertriglyceridemia, which is also associated with acute pancreatitis (1.3 to 3.8 percent of cases).<sup>5</sup>

The **Musculoskeletal and Connective Tissue Disorder** report (CASE 5989383) involves a 14-year-old boy with familial hypercholesterolemia who started simvastatin in Jan02 (dose increased from 10 mg to 40 mg). In Jun04, after his methylphenidate (Concerta) dose was increased from 36 mg to 54 mg, the boy developed thigh stiffness and CK of 792. Simvastatin was discontinued (methylphenidate continued) and the boy recovered. Atorvastatin 20 mg was started in Aug04, decreased to 10 mg in Jan05, and ezetimibe (Zetia) added in Jan05. In Sep05, CK was 831 without muscle complaints. In Jan06, the boy complained of muscle symptoms (including chest pain); CK was 24,265. Atorvastatin and ezetimibe were discontinued on 16Jan06 (methylphenidate continued). Three days later the CK was 3,674; on 6Feb06 CK was 218. Atorvastatin is labeled for muscle symptoms (including muscle

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<sup>5</sup> Greenberg NJ, Toskes PP. Acute and chronic pancreatitis. In: Kasper DL, Fauci AS, Long DL, Braunwalk E, Hauser SL, Jameson JL, editors. Harrison’s principles of internal medicine. 16<sup>th</sup> ed. New York: McGraw-Hill;2005. Chapter 294 (available at <http://online.statref.com>).

tenderness, or weakness, myalgia, myopathy, myositis, leg cramps, and rhabdomyolysis) and elevations in creatine phosphokinase (CK). It is not clear why the boy experienced thigh stiffness and elevated CK when his methylphenidate dose was increased. There is no documented metabolic drug interaction between methylphenidate and statins.<sup>6</sup>

Methylphenidate has been very rarely associated with neuroleptic malignant syndrome (NMS) – that can lead to rhabdomyolysis. However, although this boy presented with muscle stiffness and increased CK, there was no mention of other common NMS-associated symptoms such as hyperthermia. In regards to the boy's redevelopment of muscle symptoms and elevated CK while taking atorvastatin and ezetimibe, the atorvastatin labeling does not mention a drug interaction between statins and ezetimibe. There is an FDA-approved statin-ezetimibe product, Vytorin (ezetimibe/simvastatin) on the market, for which myalgia was reported more frequently as an adverse reaction compared to monotherapy with ezetimibe or simvastatin (see ADVERSE REACTIONS). There are also published case reports of muscle events attributed to a possible association between ezetimibe and statins.<sup>7,8</sup>

Three reports involved **in utero exposures**. The first (CASE 4162461) involves a woman (age unknown) on atorvastatin 40 mg daily for about a year, which was discontinued 8 weeks into her pregnancy. The woman reported her male infant was born blind on 1/1/04. The second (CASE 5928839) involves a 34-year-old female on atorvastatin (duration unknown, discontinued 2Nov04), glimepiride, and metformin, with gestational diabetes mellitus; the fetus developed a single functional kidney, congenital hepatomegaly and stillbirth (1/1/04). The third (CASE 6103440) involves a 32-year-old man who took atorvastatin 10 mg daily two to three months before conception, and reported his daughter was "born with myopathy." Statins are contraindicated during nursing mothers and pregnancy (Pregnancy Category X) because of their ability to lower cholesterol and cholesterol byproducts necessary during fetal development.

Three reports involved **accidental ingestion** of atorvastatin. The first (CASE 4032531) involved a 14-year-old boy who took one each of his father's medications (including atorvastatin, gemfibrozil, metformin, verapamil, and oxycodone). The child was admitted to the hospital for one night; the glucose was 83 and treated with 10 percent dextrose. The second (CASE 4100890) involved a 2-year-old girl who experienced two seizures (witnessed by the mother) following possible ingestion of rosiglitazone, bupropion, metformin and atorvastatin. Laboratory testing revealed the glucose, CBC, and electrolytes were within normal limits, and no evidence of toxic exposure was identified by the physician. The third (CASE 4167846) involved a 10-year-old girl who mistakenly received a package of atorvastatin (instead of or in addition to phenytoin) and took one dose daily for three days. On the third day, the child experienced "syncope crisis" and was admitted to the hospital. The child continues on phenytoin, but other outcome information was not provided.

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<sup>6</sup> Lexi-Comp (Lexi-Interact On-Line). Methylphenidate: interacting categories. 2006. Available at [www.lexi-comp.com](http://www.lexi-comp.com).

<sup>7</sup> Simard C, Poirier P. Ezetimibe-associated myopathy in monotherapy and in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Can J Cardiol* 2006 Feb;22(2):141-4.

<sup>8</sup> Bays. H. Statin safety: an overview and assessment of the data-2005. *Am J Cardiol* 2006;97 [suppl]:6C-26C.

Since marketing approval, FDA has received one report of pediatric death (stillbirth), which was associated with maternal atorvastatin use and gestational diabetes mellitus (CASE 5928839, described above under in utero exposures, foreign report, received Nov05).

Characteristics for all the pediatric atorvastatin cases (n=24) found in the AERS database are described in Table 6 above and a summary of each case is provided in ATTACHMENT 1.

### 5.3 Limitation of AERS

It is possible there are additional pediatric atorvastatin adverse event reports. The search of the AERS database for atorvastatin pediatric reports identified a large percentage of reports with unknown age (see Tables 4 and 5). In addition, the voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the United States reflects underreporting and duplicate reporting. For any given report, there is limited certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

## 6. PEDIATRIC UTILIZATION DATA

The number of atorvastatin pediatric prescriptions dispensed in retail pharmacies remains less than 0.1 percent of the total number of prescriptions dispensed in retail pharmacies (see Table 7). Use in the pediatric population appears to be decreasing over the past few years, but the numbers are small and based on projected values which may not represent actual trends. Furthermore, the decrease could be due to increased use of mail service (and mail service prescriptions aren't reflected in Table 7 below).

**\*\*The table below contains proprietary drug use data obtained by under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\***

<b>Table 7. Total Number of Atorvastatin Prescriptions Dispensed in Retail Pharmacies* Nationwide (By Year Since 2002).</b>				
Source: Verispan, Vector One®: National (VONA), Queried Aug 31, 2006				
Age (in years)	Number of Prescriptions By Year			
	2002	2003	2004	2005
<b>0-16</b>	36,668	36,894	37,101	32,381
0-1	4,295	2,420	2,524	1,979
2-5	10,362	10,939	8,393	6,072
6-16	22,011	23,535	26,184	24,330
<b>17+</b>	56,600,352	58,468,218	62,176,009	62,806,963
<b>UNSPEC.</b>	158,381	186,715	327,376	379,279
<b>Total</b>	56,795,401	58,691,827	62,540,486	63,218,623

\*Doesn't include mail service or long-term care. Numbers may be lower than previous consult that used data from IMS Health (which included mail service prescription data).

## 7. SUMMARY AND RECOMMENDATIONS

The review of the few (n=12) atorvastatin pediatric reports in the AERS database did not identify adverse events unique to the pediatric population. However, the review was limited by the few number and incompleteness of reports. In adults, liver dysfunction and muscle-related events (such as myopathy, myalgia, and rhabdomyolysis) are known, labeled risks associated with all statins. In April 2006, following a comprehensive assessment of statin safety (primarily in adults), the National Lipid Association Safety Assessment Task Force concluded:<sup>9</sup> 1) Dose-related, asymptomatic elevations in ALT or AST more than three times the upper limit of normal are seen with all statins. These elevations are typically transient and resolve spontaneously. 2) Liver dysfunction or liver failure associated with statin use cannot be ruled out. There are published reports of statin-induced hepatotoxicity and FDA has received statin reports of liver dysfunction and liver failure. It is possible liver failure is an idiosyncratic reaction that occurs very rarely with statin therapy, but it is also argued that the rate of liver failure in those individuals taking statins is about the same as the population not taking statins. 3) The most prevalent and significant adverse events associated with statin therapy are related to muscle symptoms or signs. In a practice setting, the incidence of muscle complaints associated with statin use ranges from 0.3 to 33 percent (1.5 to 3 percent in clinical trials). Myalgia (muscle pain or soreness) is the most common muscle symptom, and more likely to occur at higher statin doses or other situations resulting in elevated blood statin levels (such as that seen with drug interactions). Serious muscle toxicity associated with statin therapy is rare (rhabdomyolysis occurs in 1.6 patients per 100,000 person-years; myopathy in 5 patients per 100,000 person-years). 4) For individuals requiring statin therapy, the benefit outweighs the risk.

The current labeling for atorvastatin outlines liver, muscle, and pregnancy risks, and provides recommendations for monitoring and managing these risks by reducing or withdrawing statin therapy or avoiding drug interactions.

The National Cholesterol Education Program (NCEP) recommends lipid-lowering drug therapy for children 10 years and older if, after an adequate trial of diet therapy, the LDL cholesterol remains  $\geq 190$  mg/dL or the LDL cholesterol remains  $>160$  mg/dL and there is a family history of premature CVD or the presence of two or more other CVD risk factors.<sup>10</sup> In the United States, available lipid-lowering drugs include: bile acid sequestrants, niacin or nicotinic acid, fibrates, intestinal cholesterol absorption inhibitors (ezetimibe), omega fatty acids (omega-3-acid ethyl esters), and statins. Of these agents, the bile acid sequestrants and statins are most commonly used in children.<sup>11</sup> However, bile acid sequestrants are associated with intolerability (poor palatability and gastrointestinal upset) and modest lipid-lowering effects. The statins are supported by a growing body of pediatric clinical trial data, significant lipid-altering effects, improved

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<sup>9</sup> McKenney JM. Report of the National Lipid Association's Statin Safety Task Force. *Am J Cardiol*. 2006 Apr 17;97(8 Suppl 1):S1-S98.

<sup>10</sup> American Academy of Pediatrics. National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 1992;89(3 Pt 2):525-584.

<sup>11</sup> Holmes KW, Kwiterovich PO. Treatment of dyslipidemia in children and adolescents. *Curr Cardiol Rep*. 2005 Nov;7(6):445-56.

tolerability compared to other lipid-lowering agents, and widespread exposure in adults (in 2005 there were more than 140 million prescriptions dispensed in the United States<sup>12</sup>).<sup>11,13,14</sup> Niacin or nicotinic acid products are not routinely used in children due to significant adverse effects such as flushing and myopathy. The fibrates are generally reserved for children with hypertriglyceridemia at risk for pancreatitis,<sup>13</sup> and the use of omega fatty acids are limited by lack of published pediatric studies. Ezetimibe (approved by FDA in 2002) has been shown efficacious in children with homozygous familial hypercholesterolemia or sitosterolemia, but is not yet approved by FDA for use in children.<sup>11</sup>

In summary, the benefit of statins in adults is well documented, and there is growing evidence that statins are efficacious and well tolerated in the pediatric population. However, liver and muscle adverse events remain important risks associated with statin therapy. In addition, it is likely that pediatric patients who require lipid-lowering drugs may use these drugs for many years, and the long-term safety profile of statins (including use during the growth period) is unknown. There are too few reported adverse events in any one area to make a conclusion regarding safety signals unique to the pediatric population. The Division of Drug Risk Evaluation will continue to monitor.

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<sup>12</sup> IMS Health. Top-line industry data. 2006 (cited Jul 27, 2006). Available at: [http://www.imshealth.com/ims/portal/front/indexC/0,2773,6599\\_5264\\_0,00.html](http://www.imshealth.com/ims/portal/front/indexC/0,2773,6599_5264_0,00.html)

<sup>13</sup> McCrindle BW. Hyperlipidemia in children. *Thrombosis Research*. 2006;118:49-58.

<sup>14</sup> Rodenburg J, Vissers MN, Daniels SR, Weigman A, Kastelein JJ. Lipid-lowering medications. *Pediatr Endocrinol Rev*. 2004 Nov;2 Suppl 1:171-80.

Jo Wyeth, Sept 6, 2006  
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8. **ATTACHMENT 1: Summary of Pediatric Atorvastatin (Lipitor) Cases in AERS Database, Categorized by Date Received (Marketing Approval Through AERS Cutoff Date of August 22, 2006)**

RECVDATE	CSENUM	DESCRIPTION
12/31/1997	3005937	Foreign physician report of premature infant (1.5 kg) born with cleft lip palate on [redacted]. The infant's 39-year-old father took atorvastatin 10 mg daily since 7Nov96. The father has two other children with no congenital anomalies. The mother has a history of three term pregnancies.
7/2/1999	3381071	U.S. consumer reports her 15-year-old son experienced dizziness and upset stomach while taking atorvastatin (dose and duration unknown).
2/29/2000	3441275	U.S. physician reports that a female infant (3.695 kg) was born on [redacted] with esophageal atresia and esophageal fistula. The mother took atorvastatin (dose unknown) for three weeks during her pregnancy. The mother has another daughter with the same condition (but didn't take atorvastatin during that pregnancy). Infant had a thoracotomy with division of tracheoesophageal fistula and primary esophageal anastomosis, and discharged from the hospital with gastrostomy tube.
3/17/2000	3382093	U.S. physician reports normal male infant (3.911 kg) was born on [redacted]. The infant's 25-year-old mother took atorvastatin 20 mg daily (duration unknown, but discontinued on 11May99) and has a history of smoking (1PPD) and one live birth with anencephaly. During the pregnancy, the unborn fetus (trimester not specified, reported initially in Oct99) developed choroid plexus cysts, which resolved.
11/14/2000	3441675	Literature report from Germany (Vagt A, Kastendieck C. Probable congenital anomaly after exposure to atorvastatin in early pregnancy ) of an infant born on [redacted] with aplasia of left hand, wrist and distal forearm. The infant's 39-year-old mother had a history of smoking during pregnancy (10-15 cigarettes per day) and had been taking atorvastatin 10 mg daily for 2 years (discontinued 7th week of pregnancy).
12/19/2000	3587099	Foreign physician report of a male infant (3.8 kg) born on [redacted] with cleft palate. The infant's 26-year-old mother had been taking atorvastatin 40 mg daily for almost one year (discontinued 4th week of pregnancy).
12/26/2000	3588860	U.S. investigator reports 12-year-old female study patient (Study C981-147-010) with history of mild to moderate depression, self-mutilation, ADHD, and difficulty being back in school (on fluoxetine and hydroxyzine since 12Jul00), was taking atorvastatin (10 mg daily for 24 days [24Mar00 through 16Apr00] and 20 mg daily or placebo for following 137 days) for familial hypercholesterolemia and was hospitalized on [redacted] (Study Day 161) with depression (including suicidal ideations). Treated with valproic acid and venlafaxine, and discharged on [redacted].

RECVDATE	CSENUM	DESCRIPTION
5/8/2001	3607139	U.S. pharmacist reports an 8-year-old female experienced a possible accidental ingestion of atorvastatin 10 mg (one dose) on 2Feb01. The child's mother reported the child was "acting nervous and her legs were shaky." The pharmacist reports the ingestion was "being doubted as truthful" and the "shaky leg" comment was attributed to what the mother read on the counseling information for atorvastatin. The poison control center classified as "benign" ingestion with possible gastrointestinal upset with "no adverse event."
6/6/2001	3660134	U.S. consumer reports she became pregnant while taking clonazepam (continued throughout pregnancy), atorvastatin (dose and duration unknown), albuterol, fluconazole, and azithromycin. At 29-weeks, she was hospitalized for aspiration pneumonia and treated with azithromycin and prednisone. In _____ her blood pressure _____ and an emergency caesarean section was performed. The newborn's (gender unknown) birth on _____ was 3.5 weeks early (weight: 2.5 kg). The infant was not breathing at birth (APGAR Score: 6 at 1 minute), but started breathing shortly afterwards. At the time of report (Jun01), the baby was thriving and no abnormalities were noted.
7/3/2002	3768514	U.S. consumer reports his 17-year-old son with history of Mauriac syndrome, type 1 diabetes, ESRD, renal transplant, flow murmur, and enlarged spleen, liver and bladder since birth, started taking atorvastatin in Jul01 for hypercholesterolemia. During the course of atorvastatin therapy, the boy developed elevated ALT and AST levels (Oct01: AST 80, ALT 84; Jan02: AST 145, ALT 149; 12Feb02: AST 82, ALT 121). Atorvastatin DC on 14Feb02. On 25Feb02, AST was 74 and ALT was 75 (cholesterol 277).
7/12/2002	3805234	U.S. physician reports twin B was born _____ at 32 weeks, 5 days gestation with problems secondary to prematurity. No anomalies were noted. The twin's 30-year-old mother discontinued atorvastatin at approximately six weeks gestation.
7/12/2002	3818064	U.S. physician reports twin B was born _____ at 32 weeks, 5 days gestation with problems secondary to prematurity. No anomalies were noted. The twin's 30-year-old mother discontinued atorvastatin at approximately six weeks gestation.
11/6/2003	4032531	RADARS reports a 14-year-old autistic male accidentally ingested one each of his father's medications: oxycodone, gemfibrozil, metformin, atorvastatin (dose unknown), and verapamil on 30Aug03. Child was admitted to the hospital and reported stable. Laboratory tests revealed glucose of 83, which was treated with 10 percent dextrose. Child discharged the following day on _____.
3/4/2004	4100890	U.S. physician reports a 2-year-old female experienced two seizures (witnessed by mother) following the possible accidental ingestion of rosiglitazone 2 mg tablet, bupropion 100 mg tablet, metformin, and/or atorvastatin 10 mg tablet. Glucose, CBC and electrolytes were WNL, and there was no evidence of ingestion or toxic exposure.

RECVD DATE	CSENUM	DESCRIPTION
6/21/2004	4162461	Foreign consumer report of a male infant born blind on _____. The mother (age unknown) was taking atorvastatin 40 mg daily about a year before she came pregnant (discontinued at about 8 weeks gestation).
6/30/2004	4167846	Foreign consumer report of a 10-year-old female with history of dysrhythmia and taking phenytoin, mistakenly took atorvastatin (dose unknown) once daily for three days. The child experienced a "syncope crisis" and was hospitalized. The physician informed the consumer that the child "lost her legs movements in that moment." The child continues on phenytoin.
7/29/2004	4188752	U.S. physician reports a 14-year-old patient (gender unknown) experienced bone marrow suppression while taking atorvastatin for homozygous familial hypercholesterolemia. No additional information provided.
10/25/2004	5659245	Foreign healthcare professional report of a 4-year-old male with history of "myocardial ischemia" was taking both atorvastatin 10 mg daily (since Apr04) and simvastatin 20 mg daily (since Mar04). The child developed "marked bronchospasm" in Mar04, which was "reversible and present 3 times on rechallenge." The patient recovered from the bronchospasm in May 2004. The outcome in regards to both atorvastatin and simvastatin is unknown.
11/23/2004	5697315	U.S. physician reports 16-year-old female with no history of nutritional deficiencies experienced fatigue and hemoglobin of 7 within 11-12 months of starting atorvastatin 10 mg daily for familial hypercholesterolemia. The fatigue was attributed to iron deficient anemia and treated with iron supplements. She continues on atorvastatin.
1/14/2005	5720150	Foreign physician report of 16-year-old male with familial hypercholesterolaemia who developed haemoptysis in Nov04 about six months after starting nicotinic acid and atorvastatin 10 mg daily (which was increased to 20 mg daily 2 months before event). The child was hospitalized and bronchoscopy showed diffuse pulmonary alveolar haemorrhage. Echocardiogram showed cardiomegaly and EF was 37%. Both atorvastatin and nicotinic acid were DC.
1/28/2005	6103440	U.S. consumer reports his daughter was born on _____ with myopathy. The 32-year-old consumer took atorvastatin 10 mg for two to three months before conception. No additional information provided.
11/16/2005	5928839	Foreign regulatory report of female infant (33 weeks gestation) who developed single functional kidney, congenital hepatomegaly and stillbirth _____. The 34-year-old mother developed diabetes mellitus during pregnancy and was treated with gliclazide, metformin, insulin, and atorvastatin (discontinued 2Nov04 at about 24 weeks gestation).
11/23/2005	5952060	U.S. consumer reports her 16-year-old daughter with history of diabetes and hypercholesterolemia, was taking atorvastatin 30 mg daily for about two years and was diagnosed with pancreatitis in Nov04 (which "seemed to go away but came back in Jan05"). Along with atorvastatin, the child was also taking oral contraceptives, "homeopathic detox and stomach pain medications" As of 20Jan05, the child continues to take atorvastatin and the event persists.

RECVDATE	CSENUM	DESCRIPTION
3/10/2006	5989383	Foreign physician report of a 14-year-old, 100-kg male who experienced elevated creatine phosphokinase (CK) levels while taking lipid-lowering drugs for familial hypercholesterolemia and methylphenidate (Concerta). The child started simvastatin in Jan02 (dose increased from 10 mg to 40 mg). Methylphenidate increased to 54 mg in Jun04 and the child experienced thigh stiffness (CK: 792). Simvastatin DC and event resolved. In Aug04, atorvastatin 20 mg started; dose decreased to 10 mg in Jan05 and ezetimibe added (dose unknown). In Sep05, CK was 831, but no muscle symptoms were apparent. In Jan06, child complained of muscle symptoms (including chest pain). CK was 24,265. Atorvastatin DC. 19Jan05, CK was 3,674 and 218 on 6Feb06.